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THERAPEUTIC USES OF BOTULINUM TOXIN

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BOTULISM had been recognized by the 18th century, but the observation that a toxin produced by an anaerobic organism might be responsible for food poisoning was not made until 1897.[1] Although seven immunologically distinct toxins have since been identified, only types A, B, and E have been linked to cases of botulism in humans.[2,3] Botulinum toxin type A (hereafter referred to as botulinum toxin), one of the most lethal biologic toxins, has been found to be of therapeutic value in the treatment of a variety of neurologic and ophthalmologic disorders.[4] The Food and Drug Administration recently approved botulinum toxin (Oculinum) as a therapeutic agent in patients with strabismus, blepharospasm, and other facial-nerve disorders, including hemifacial spasm. In this article we review the rationale for the use of botulinum toxin and the accumulated experience with the agent in these and other disorders.

MECHANISMS OF ACTION OF BOTULINUM TOXIN

The neurotoxic component of botulinum toxin has a molecular weight of only 150,000, but the toxin forms a complex with nontoxic proteins and hemagglutinin.[2] The toxin exerts its paralytic action by rapidly and strongly binding to presynaptic cholinergic-nerve terminals.[2-5] The toxin is then internalized and ultimately inhibits the exocytosis of acetylcholine by decreasing the frequency of acetylcholine release. The treatment of muscle with botulinum toxin results in an accelerated loss of junctional acetylcholine receptors.[6] Paralysis and a nearly complete decline of miniature end-plate potentials occur within a few hours after the injection of botulinum toxin.[7,8] The delay in the onset of clinical effect may be related in part to the spontaneous release of acetylcholine.[9] The muscle becomes functionally denervated, atrophies, and develops extrajunctional acetylcholine receptors.[10] Within two days after muscle exposure to the toxin, the axon terminal begins to sprout, and the proliferating branches then form new synaptic contacts on the adjacent muscle fibers.[5,11]

Although it is likely that the clinical effect of botulinum toxin is due primarily to its action at the neuromuscular junction, after peripheral administration it can enter the central nervous system.[12,13] If applied directly, botulinum toxin binds to preparations of brain synaptosomes and nonspecifically inhibits the release of transmitters.[14] When injected into mammalian gastrocnemius muscle, it is transported to the spinal cord by retrograde axonal transport and can later be detected in the appropriate spinal-cord segments.[15] Intraspinal transfer is evidenced by the subsequent appearance of botulinum toxin in the contralateral half-segment.[16] In the cord, the toxin appears to block recurrent inhibition mediated by the Renshaw cells.[16]

Cultures of clostridial botulinum toxin are established in a fermenter, grown and harvested by acidification and centrifugation, and further purified and processed for commercial use.[4] The standard unit for measuring the potency of commercially available toxin is derived from a mouse assay.[17,18] In this assay, 1 U of botulinum toxin is the amount that kills 50 percent of a group of 18 to 20 female Swiss–Webster mice (the LD_{50}). The toxin available in the United Kingdom (Dysport) is much more potent than that available in the United States. One nanogram of the British toxin contains 40 mouse units, whereas 1 ng of the American toxin contains 2.5 mouse units.[19] The difference in potency between the two forms of the toxin may explain the difference in results, particularly the apparently higher incidence of side effects with the more potent British toxin. With the American form of the toxin, the LD_{50} in monkeys after intravenous[20] or intramuscular[21] administration has been estimated to be 40 U per kilogram of body weight. The dosages used in human therapeutic applications are roughly proportional to the mass of the muscle being injected and are much lower than the estimated LD_{50}.

Until recently, antibodies had not been detected in humans exposed to botulinum toxin either by food poisoning or after therapeutic injections.[22] A cumbersome in vivo mouse neutralization assay has been used to detect serum antibodies to botulinum toxin.[23] The presence of a neutralizing (blocking) antibody is suggested if the mice remain healthy after the injection of both serum and botulinum toxin. Unprotected mice die, and this result constitutes a negative assay. Enzyme-linked immunosorbent assays for the detection of antibody have been developed,[24,25] but their specificity and clinical correlation with resistance to treatment with botulinum toxin have not yet been demonstrated. Clinical resistance to the effects of subsequent injections of botulinum toxin has been demonstrated in some patients after repeated treatment, and it has

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been correlated with the presence of antibodies to botulinum toxin detected by the bioassay.[26]

Clinical Applications of Botulinum Toxin

Strabismus and Other Disorders of Ocular Motility

Botulinum toxin was initially used to weaken extraocular muscles.[27] The toxin was then introduced for the treatment of strabismus as an alternative to conventional incisional surgery.[28-31] The injections are performed under electromyographic guidance with a Teflon-coated needle to ensure accurate placement in the extraocular muscle. Most patients are treated in the office with topical anesthesia; children under seven years of age may require light ketamine anesthesia and restraint.[30] Follow-up studies up to five years after the injection show that 85 percent of the patients available for reassessment had satisfactory improvement.[30,31] Side effects, including partial ptosis and secondary vertical deviations, are usually transient and do not result in amblyopia. Biglan et al.[32] presented a less optimistic outcome for infantile esotropia; in only 33 percent of the patients in their study was the condition adequately controlled with botulinum toxin. Prospective, randomized clinical trials are needed to answer the question of whether therapy with botulinum toxin is a substitute for or adjunct to surgery.

Botulinum toxin has been injected into extraocular muscles to treat comitant strabismus,[28,32] vertical strabismus,[33] lateral rectus palsy,[34,35] and nystagmus.[36] Dunn et al.[37] reported favorable results with botulinum toxin in a group of 27 patients with dysthyroid myopathy, but 16 ultimately required surgery.[31] Long-term follow-up will be necessary to evaluate these pilot studies.

Dystonias

The therapeutic scope of botulinum toxin has continued to expand, and it now includes a variety of neurologic disorders associated with inappropriate muscular contractions or spasms. The chief therapeutic use is for the treatment of focal dystonias. Dystonia is a syndrome dominated by involuntary sustained (tonic) or spasmodic (rapid or clonic), patterned, repetitive muscle contractions, frequently causing twisting (e.g., torticollis), flexing or extending (e.g., writer's cramp and retrocollis), and squeezing (e.g., blepharospasm) movements or abnormal postures.[38] Anatomical localization of a functional abnormality in the rostral brain stem, basal ganglia, or both is supported by physiologic studies and by the observation that damage to these regions can produce dystonia.[38,39] Clinical, pharmacologic, and biochemical studies have provided evidence for noradrenergic preponderance in dystonia.[40,41] This neurochemical abnormality may be genetically determined. The most important advance in our knowledge of genetic dystonia has been the identification of a marker for idiopathic autosomal dominant dystonia in the q32–q34 region of chromosome 9.[42]

In addition to sporadic and genetic dystonias, there are many secondary dystonias due to specific causes, such as Wilson's disease, metabolic and neurodegenerative disorders, a variety of brain lesions, toxins, and the use of either dopaminergic or antidopaminergic drugs (e.g., tardive dystonia).[38] Besides primarily central causes, which presumably account for the vast majority of dystonias, there is convincing evidence that they can be caused or triggered by injury to a peripheral nerve or root.[43]

If no specifically treatable causes of dystonia can be identified, then patients can be offered only symptomatic relief (Table 1). Although medications can ameliorate dystonic symptoms in some patients, the majority fail to obtain satisfactory relief. A scientific rationale for many of the pharmacologic approaches is lacking. Muscle relaxants and anticholinergic drugs, particularly trihexyphenidyl, are the most effective.[44,45] In more advanced cases, anticholinergic drugs can be combined with other drugs, such as pimozide (a dopamine-receptor–blocking drug) and tetrabenazine (a drug that depletes dopamine and blocks dopamine receptors).[46] The dopamine-receptor–blocking drugs, however, can produce a variety of potentially chronic and disabling side effects, particularly tardive dyskinesia and other drug-induced movement disorders.[47] Tardive side effects have not been reported with tetrabenazine, but this drug is not generally available in the United States. Up to 10 percent of patients with an onset of dystonia in childhood or adolescence have marked improvement with levodopa.[48] In patients with focal dystonia and in some patients with segmental dystonia unresponsive to

Table 1. Suggested Therapeutic Guidelines for Patients with Dystonia.

Type of Dystonia	Treatment
Focal	
Blepharospasm	Clonazepam, lorazepam
	Trihexyphenidyl, ethopropazine
	Botulinum toxin
	Orbicularis oculi myectomy
Cervical dystonia (spasmodic torticollis)	Trihexyphenidyl, ethopropazine
	Diazepam, lorazepam, clonazepam
	Botulinum toxin
	Tetrabenazine
	Cyclobenzaprine
	Carbamazepine
	Cervical rhizotomy
Oromandibular dystonia	Baclofen
	Trihexyphenidyl, ethopropazine
	Reserpine, tetrabenazine (with lithium)
	Botulinum toxin
Spasmodic dysphonia (laryngeal dystonia)	Botulinum toxin
	Trihexyphenidyl, ethopropazine
	Propranolol
	Primidone
Task-specific dystonias	Benztropine, trihexyphenidyl
	Botulinum toxin
	Occupational therapy
Segmental and generalized (tremor)	Levodopa (in children and young adults)
	Trihexyphenidyl, ethopropazine, benztropine
	Diazepam, lorazepam, clonazepam
	Baclofen (oral or intrathecal)
	Carbamazepine
	Tetrabenazine (with lithium)
	Triple therapy: tetrabenazine, pimozide, trihexyphenidyl
	Surgery: rhizotomy, myectomy, thalamotomy

pharmacologic therapy, injections of botulinum toxin into the contracting muscles provide the most effective, albeit temporary, relief.

Blepharospasm

Blepharospasm is a form of focal dystonia manifested by intermittent or sustained closure of the eyes due to involuntary contractions of the orbicularis oculi. It is often accompanied by spasms of facial, oromandibular, pharyngeal, laryngeal, and neck muscles (cranial–cervical dystonia or Meige's syndrome).[49,50] The severity of symptoms may range from increased blinking to functional blindness as a result of sustained, sometimes painful, forceful closure of the eyelids. Medications such as clonazepam, lorazepam, baclofen, and trihexyphenidyl provide symptomatic benefit in up to a third of these patients, but the degree of improvement is often unsatisfactory or is achieved at the expense of adverse reactions. Surgical treatments include orbicularis myectomy, facial-nerve sectioning, and brow lift (Table 1). Although the majority of patients seem to respond to surgery, some have complications, including exposure keratitis, local sensory impairment, lower-lid ectropion, ptosis, and eyelid necrosis, and the blepharospasm may recur within months after the surgery.

The beneficial effects of injections of botulinum toxin in the treatment of blepharospasm have been demonstrated in one controlled[51] and several open[52-56] trials. The reported benefits varied, depending on the methods of assessment and definitions of improvement. In most studies, however, there was moderate-to-marked symptomatic and functional improvement in 70 to 90 percent of the treated patients. The time between the injection and the onset of improvement was about two to five days, and the benefits lasted an average of 3½ months. There was no demonstrable decline in efficacy after repeated injections. The most common adverse effects, all self-limited, included ptosis, blurred vision, diplopia, local pain and swelling, entropion, and increased tearing.[57-59] Because of its proved safety and efficacy, botulinum toxin is now considered a primary form of therapy for blepharospasm.[60]

In addition to blepharospasm, we and others have injected botulinum toxin into the eyelids of patients with parkinsonism who have levodopa-induced blepharospasm and "apraxia of eyelid opening" triggered by blepharospasm.[61,62] Ptosis induced by injecting botulinum toxin into the levator palpebrae superioris has been used to protect the cornea[63] and to treat eyelid entropion,[64] intractable orbicularis myokymia,[65] and other eyelid disorders.

Cervical Dystonia (Spasmodic Torticollis)

Cervical dystonia is a focal dystonia affecting the neck muscles that causes patterned, repetitive, clonic (spasmodic) head movements or tonic (sustained) abnormal postures of the head as a result of twisting (torticollis), tilting toward one shoulder (laterocollis), flexing (anterocollis), or extending (retrocollis) the neck. Torticollis is the most common form of dystonic head deviation, but the majority of patients with cervical dystonia have a combination of these abnormal postures.[66] Although spontaneous remissions occur in up to 20 percent of patients, the remissions are usually transient and nearly all patients eventually relapse.[67] In approximately one third of all patients with cervical dystonia, there is ultimately involvement of contiguous body parts, such as the oromandibular region, shoulder, and arm.

Physical therapy and relaxation techniques are of limited benefit to patients with severe cervical dystonia, but may be useful in preventing permanent contractures. When properly fitted, cervical braces may help some patients maintain a primary position. In up to half these patients, pharmacotherapy provides some benefit, but the reduction in neck spasms is usually not sufficient to improve the patients' function and control of neck movement (Table 1). Surgical therapy, such as selective peripheral denervation, may offer relief to carefully selected patients, but the results vary considerably, and some patients eventually relapse.[68]

The efficacy and safety of botulinum toxin in the treatment of cervical dystonia have been demonstrated in several controlled[69-72] and open[54,56,73-75] studies. In one double-blind, placebo-controlled study of 55 patients with cervical dystonia, 61 percent improved after the injection of botulinum toxin.[72] In an open longitudinal study of 303 patients with medically intractable cervical dystonia, injections of botulinum toxin into 1818 muscles in 844 treatment sessions resulted in substantial improvement in function and control of head and neck movements in 92 percent of the patients.[75] Furthermore, 93 percent had marked relief of their neck pain. The average latency between the injection and the onset of improvement (and muscle atrophy) was 1 week, and the average duration of maximal improvement was 3½ months. The total duration of improvement, however, was about six weeks longer. Most patients required injections every four to six months. In this study, 14 percent of the patients did not improve after one or more treatments, and 6 percent had no response to repeated treatment. Similar results have been reported in other studies of injections of botulinum toxin in patients with cervical dystonia.[73,74]

To determine which variables predict the response to botulinum toxin, clinical correlates were analyzed in 242 patients with cervical dystonia.[26] Patients with longstanding dystonia responded less well than those who were treated relatively early, possibly because prolonged dystonia produces contractures. Twenty-eight percent of the patients had complications such as swallowing difficulties, neck weakness, and nausea sometime during treatment (some patients had up to 12 treatments in five years). Dysphagia, the most common complication, was reported in 14 percent of 659 visits, but in only five patients was this prob-

lem severe enough to require a change to a soft or liquid diet. Most complications resolved spontaneously, usually within two weeks. An injection into one or both sternocleidomastoid muscles was associated most frequently with dysphagia. Women, possibly because of their thinner necks, were at higher risk for swallowing difficulties. Dysphagia may be a dose-related side effect. In two studies of botulinum toxin in cervical dystonia conducted in England, where a more potent preparation of the toxin is used, the frequency of dysphagia ranged from 28 to 90 percent.[71,74] Videofluoroscopic studies have shown that up to one third of patients with cervical dystonia may have some abnormalities of swallowing even before therapy with botulinum toxin.[76] These patients may be at increased risk for dysphagia after treatment with botulinum toxin.

Since the introduction of botulinum toxin into clinical use, the possibility that blocking antibodies may develop has been one of the most feared consequences of long-term treatment. In the study of clinical-response correlates in 242 patients with cervical dystonia,[26] none of the 23 patients categorized as "responders" who were randomly selected to have their serum tested by the mouse bioassay had antibodies to botulinum toxin. In contrast, 5 of the 14 patients (36 percent) in whom treatment became ineffective after repeated injections of botulinum toxin had anti–botulinum toxin antibodies.[26] These seropositive patients, besides deriving no benefit from subsequent injections, also had no adverse effects, further supporting the notion that they had blocking anti–botulinum toxin antibodies. This study suggests that a few patients eventually lose their ability to respond because blocking antibodies develop. The presence of antibodies to botulinum toxin seems to depend on the total dose of toxin administered and on the assay method. Although there is a good correlation between the presence of antibodies to botulinum toxin as determined by the mouse bioassay and the lack of beneficial effect of injections of botulinum toxin, there is little or no correlation between the presence of antibodies as measured by enzyme-linked immunosorbent assay and the clinical response.[24,25] It is likely that patients with antibodies against botulinum toxin will respond to injections with other botulinum toxins that are immunologically distinct from type A.

The most important determinants of a favorable response to treatment with botulinum toxin are proper selection of the involved muscles and the dose. Initially, we and others used electromyography to assist in selecting the most strongly contracting muscles. However, as we gained more experience, we found that electromyography is not critical, and we now rely primarily on careful examination of the patients. Palpation of the contracting muscles while the patients place their head in the position most favored by the dystonic pulling of the neck muscles is particularly helpful. Our results are similar to those of other investigators who still use electromyography for the selection of muscles and for guidance during the injection.[77,78] We therefore now recommend electromyography only in obese patients or when the involved muscles are difficult to identify by palpation.

Oromandibular Dystonia

Oromandibular dystonia involves the masticatory, lower facial, and tongue muscles. It results in trismus, bruxism, involuntary tongue movement, and opening, closure, or deviation of the jaw.[50,79] Anticholinergic drugs, baclofen, benzodiazepines, and tetrabenazine may be helpful, but pharmacotherapy is usually ineffective in this form of dystonia (Table 1).[45,46,50]

Injections of botulinum toxin into the masseter, temporalis, and internal pterygoid muscles result in reduction in the oromandibular and lingual spasms and an improvement in chewing and speech in approximately 70 percent of patients with jaw closure due to oromandibular dystonia.[54,56,80] Some patients (about 10 percent) have no improvement, and some have transient weakness of the jaw, impeding closure. Treatment of dystonia causing jaw opening and lateral-deviation dystonia requires detailed knowledge of the local anatomy and management of complications. Up to 50 percent of patients with these forms of dystonia benefit from injections into the submental muscle complex or the external pterygoid muscles, but many have mild dysphagia. Aspiration pneumonia has occurred, rarely requiring a temporary gastrostomy for feeding. Complications, particularly oral dysphagia requiring a liquid diet, occur in approximately half the patients treated for lingual dystonia. In selected patients, however, treatment with botulinum toxin has resulted in marked relief of disability.[56,80] For most patients with jaw-closing dystonia, and many patients with dystonia causing jaw opening or deviation of the jaw, such treatment is preferable to pharmacotherapy.[60]

Spasmodic Dysphonia (Laryngeal Dystonia)

Spasmodic dysphonia is an action-induced laryngeal dystonia characterized by a strained, strangled, or breathy voice, frequently interrupted by voiceless pauses.[81] The common association of laryngeal dystonia with dystonia involving other segments of the body is well recognized, and many of the phenomenologic features of patients with laryngeal dystonia are similar to those of patients with more generalized dystonia.[38] Although there is growing evidence that laryngeal dystonia is a neurologic disorder, the symptoms are still frequently attributed incorrectly to psychogenic causes.

Two distinct types of laryngeal dystonia have been identified: adductor, due to approximation of the vocal folds, and abductor, due to intermittent separation of the vocal folds.[81] Some patients appear to have a combination of the two. Patients with adductor laryngeal dystonia have a voice that sounds choked, strained, or strangled and an abrupt manner of initiating and terminating their speech, resulting in short

breaks in phonation. Patients with abductor laryngeal dystonia have a voice that is breathy and whispery. Like patients with other dystonias, many patients with laryngeal dystonia have an associated voice tremor, which may be a dystonic tremor or a variant of essential tremor.[82]

Treatment of laryngeal dystonia was unrewarding before the advent of local injections of botulinum toxin. Speech and voice therapy and systemic pharmacotherapy provide little relief of symptoms. Sectioning of the recurrent laryngeal nerve produced dramatic relief of symptoms.[83] After three years, however, only 36 percent of the patients continued to have improvement and only 1 of 33 had a persistently normal voice.[84]

Since 1984, electromyographically guided injections of botulinum toxin into the vocalis complex have been used successfully in the treatment of laryngeal dystonia.[85] The diagnosis of adductor laryngeal dystonia is first confirmed by detailed neurologic, otolaryngologic, and speech–language assessment and documented by video and voice recordings and by fiberoptic laryngoscopy. The toxin is then injected through a monopolar, hollow, Teflon-coated electromyographic needle connected to a recorder by an alligator clip attached to the hub of the needle. The needle is placed in the thyroarytenoid vocalis complex by impaling the muscle through the cricothyroid cartilage, and the toxin is injected. In the protocol used by the Columbia University group, both vocal cords are injected with small doses (0.625 to 3.75 U) of toxin in an effort to decrease the degree of adduction by causing mild bilateral weakness.[85] The groups at Baylor College of Medicine[56,86] and the National Institutes of Health[87] have injected higher doses (15 to 30 U of botulinum toxin) into one vocalis complex in order to produce unilateral paralysis. Regardless of the technique, treatment with botulinum toxin usually results in 80 to 100 percent improvement in voice symptoms.[56,85-87] Side effects include transient breathy hypophonia, hoarseness, and usually clinically unimportant aspiration of fluids. Patients with adductor laryngeal dystonia who have already undergone recurrent-laryngeal-nerve section improve markedly after the injection of botulinum toxin, but the degree of benefit is somewhat less than in patients who had not undergone previous surgery.[88,89] Injections guided by electromyography into the posterior cricoarytenoid muscle have reportedly been beneficial in a few patients with abductor laryngeal dystonia.[90] Despite the occasional complication and the risk of possible reflex laryngeal stridor, botulinum toxin is currently recommended as the primary therapy for laryngeal dystonia.[60,91] Injections of botulinum toxin into the vocalis complex may also be useful in the treatment of stuttering.[92] When used by a team consisting of an otolaryngologist experienced in electromyographically guided laryngeal injections and a neurologist knowledgeable about motor disorders of speech and voice, botulinum toxin is a safe and effective treatment for spasmodic adductor dysphonia.[91]

Other Dystonias

Writer's cramp and other focal task-specific dystonias are among the most occupationally disabling of all dystonic disorders.[92-95] Previously thought to be of psychogenic origin, there is now convincing evidence that these disorders result from disturbances in fine-motor control and that they are closely linked with, or represent a forme fruste of, idiopathic torsion dystonia.[95] The results of various treatments, including various muscle-relaxation techniques, physical and occupational therapy, and medical and surgical therapies, have been disappointing. In open trials, injections of botulinum toxin into selected muscles of the hand and forearm provided effective relief.[56,96,97] In one study of 19 patients with hand dystonia, 84 percent obtained some benefit from the treatment.[97] Fine wire electrodes were used to localize bursts of muscle activation during the task, and the toxin was injected into the belly of the most active muscle. Similar beneficial results were obtained in other studies without electromyographic guidance.[56,98] Although the majority of patients noted some hand weakness, this was transient and much less disabling than the cramp. In addition to improving writer's cramp, botulinum toxin may provide relief in other task-specific disorders affecting typists, draftspersons, musicians, athletes, and other people who depend on skilled movements of their hands.

Other focal distal dystonias besides those involving the hands may be amenable to treatment with botulinum toxin. This is particularly true for patients with foot dystonia as a manifestation of idiopathic torsion dystonia and for patients with parkinsonism who may have foot dystonia as an early symptom of their disease or, more commonly, as a complication of levodopa therapy. Injections of botulinum toxin into the foot–toe flexors or extensors may not only alleviate the pain often associated with such dystonia, but also improve gait. Whether such injections will play an important part in the treatment of recurrent painful physiologic foot and calf cramps is yet to be determined.

Tremors

Tremor, an oscillatory movement produced by alternating or synchronous contractions of antagonistic muscles, is the most common involuntary movement disorder.[82] Tremor is usually mild and improves with medication in most patients, but many patients are disabled by high-amplitude and sometimes task-specific tremors that respond poorly to pharmacotherapy (Table 1).[93] In some severe cases, neurosurgical treatment (thalamotomy) may provide satisfactory relief. Tremor often accompanies dystonia,[66,82] and an improvement in dystonia is often associated with an improvement in the tremor.[99] In a pilot study of 51 pa-

tients with disabling tremors of the head and neck (42 patients) and hand (10 patients), treatment with botulinum toxin resulted in a moderate-to-marked functional improvement and a reduction in the amplitude of the tremor was noted in 67 percent of the patients.[99] The patients with head and neck tremor received about 240 U of botulinum toxin in cervical muscles, and the patients with hand tremor received approximately 50 U in forearm flexor and extensor muscles. The average interval between injection and response was 7 days, and the improvement lasted an average of 10½ weeks. Local weakness, lasting up to three weeks, occurred after the injection in 60 percent of the patients with hand tremor and in 10 percent of those with head and neck tremor. Nearly all patients, however, preferred having mild weakness to having disabling tremor. In another study, an injection of botulinum toxin into the left thyroarytenoid muscle produced marked improvement in objective and subjective measures in patients with voice tremor.[100] Encouraged by these preliminary results, we suggest that botulinum toxin may be useful for some patients with disabling focal tremor who respond poorly to pharmacologic therapy.

Hemifacial Spasm

Hemifacial spasm is a peripherally induced movement disorder involving muscles on one side of the face innervated by the ipsilateral facial nerve.[101] It is characterized by involuntary, recurrent, episodic, paroxysmal clonic twitches or tonic contractions of the eyelids and perinasal, perioral, zygomatic, and other facial muscles. The condition may be mild and only socially embarrassing, but in some patients it causes unilateral blepharospasm that can interfere with vision. It is now well established that hemifacial spasm is not of psychogenic origin, but the constant facial twitching can be psychologically distressing. Although rarely familial,[102] hemifacial spasm is usually attributed to compression or irritation of the facial nerve by an aberrant artery or abnormal vasculature in the posterior fossa. Occasionally, the facial nerve is compressed by a cerebellopontine tumor.

Although anticonvulsant medications, such as phenytoin, carbamazepine, and clonazepam, may help some patients, these and other centrally acting drugs have limited efficacy in this movement disorder. In contrast, microvascular decompression of the facial nerve often provides relief.[103] However, surgical treatment is associated with certain risks, such as permanent facial paralysis, deafness, stroke, and death.

Local injection of botulinum toxin into the involved facial muscles offers a useful alternative to surgical therapy. The spasms improve in nearly all patients, the complications are minimal and transient, and the approach can be individualized by injecting only the muscles whose contractions are most disturbing to the patient. In one study of 21 patients, the improvement in hemifacial spasm lasted an average of five months — longer than improvement in any other spasmodic disorder.[56] The only complication was transient facial weakness, which occurred in six patients. Similar results have been reported by other investigators.[54,104-108] Along with blepharospasm and strabismus, injections of botulinum toxin have been approved by the Food and Drug Administration for hemifacial spasm.

Other Potential Indications

Chemical denervation with botulinum toxin is now considered by many the treatment of choice for blepharospasm, cervical dystonia (torticollis), laryngeal dystonia (spasmodic dysphonia), certain task-specific dystonias (occupational cramps such as writer's cramp), and hemifacial spasm[31,60,109,110] (Fig. 1). The therapy may also be useful in patients with other forms of dystonia and in those with certain focal repetitive involuntary movements, such as tremor, tics, segmental myoclonus, and other hyperkinetic movement disorders.[60,109] Motor dysfunction due to abnormally increased muscle tone, such as spasticity, may also be ameliorated by treatment with botulinum toxin.[111,112] In nine patients who were severely disabled by spasticity due to chronic multiple sclerosis, injection of 400 U of botulinum toxin into the adductor leg muscles resulted in significant improvement in muscle tone.[112] The effects of botulinum toxin on spasticity in children with cerebral palsy are also being studied. Injections of botulinum toxin into the detrusor and sphincter muscles have been found to improve bladder function in patients with spinal-cord injury.[113,114] Anismus (spasm of the rectal sphincter) associated with intractable constipation has been reported to respond favorably to local injections of botulinum toxin.[115]

Further studies are needed to establish the efficacy and safety of botulinum toxin in these and other disorders associated with muscular spasms. There are no absolute contraindications to injections of botulinum toxin except a history of hypersensitivity to the toxin (none yet reported) and infection at the site of injection. Thus far, no teratogenicity has been attributed to botulinum toxin, even though several women have been injected during pregnancy. Because botulinum toxin acts on the final common pathway, spasms of any cause could be temporarily relieved by this treatment. Before the full therapeutic potential of botulinum toxin can be realized, however, well-designed controlled studies must be performed and critically analyzed for each intended indication.

It is hardly necessary to emphasize that injections of botulinum toxin should be administered only by clinicians thoroughly knowledgeable about the physiologic as well as the clinical effects of the toxin. Familiarity with local anatomy is necessary to ensure proper and safe administration. In addition to the required skills in the technique of administration, the clinicians should be experienced in the recognition and management of the various disorders for which treatment with

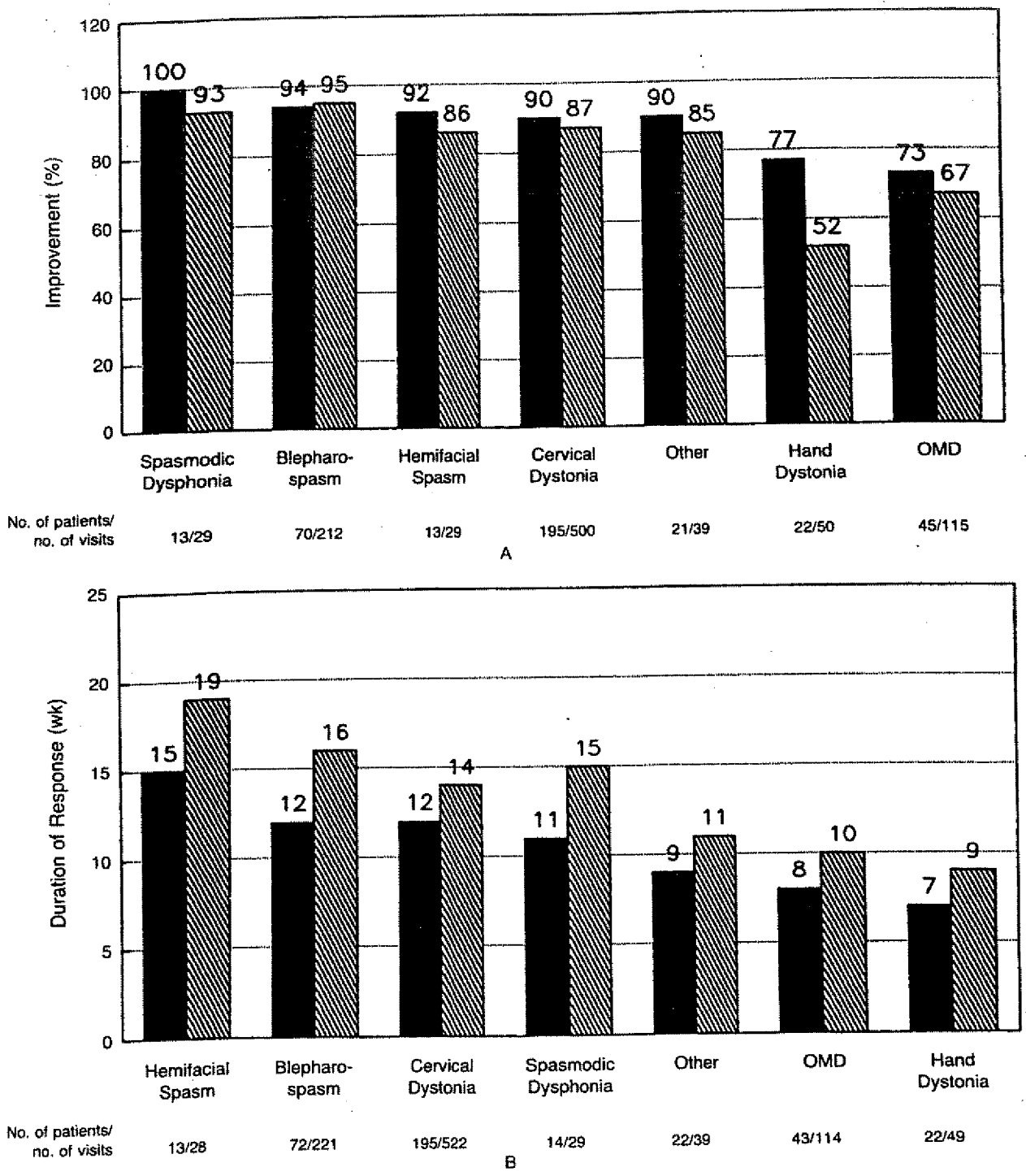

Figure 1. Effects of Treatment with Botulinum Toxin.

Panel A shows the percentage of patients whose condition improved (solid bars) and the percentage of treatment sessions or visits (hatched bars) at which improvement was noted after treatment with botulinum toxin. Improvement was defined as a global rating ≥2 on a 5-point (0 to 4) rating scale. The global rating was determined by the examiner and calculated by subtracting 1 point for mild adverse effects and 2 points for disabling effects from the overall beneficial peak effect (0 = no effect and 4 = marked improvement in severity and function).[56] Patients are arranged in the order of overall improvement: the patients with spasmodic dysphonia, blepharospasm, hemifacial spasm, or cervical dystonia responded better than the patients with hand dystonia or oromandibular dystonia (OMD).

Panel B shows the mean duration of response estimated by the patient after the injection of botulinum toxin. The maximal response (solid bars) was considered to be the duration of peak effect, and the total response (hatched bars) was considered to be the duration of any improvement. The patients with hemifacial spasm had the longest duration of response, whereas the patients treated for focal dystonia of the hands (e.g., writer's cramp) had the shortest duration of improvement.

this potent drug is planned. Finally, it is a prudent clinical practice to inform patients about the alternative therapies, limited duration of benefit, possibility of poor or no response, potential complications, and relative paucity of information on the effects of long-term treatment with botulinum toxin.

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